Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Arsenic (Inorganic Oxides) for Oral Exposure

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Office of Environmental Health Hazard Assessment
Reproductive and Cancer Hazard Assessment Section

Summary

The maximum allowable dose level (MADL) for arsenic (inorganic oxides) is **0.10 micrograms/day (µg As/d)** by the oral route of exposure. This value was derived as described below, based on a human study (Ahmad et al., 2001).

Background

This report describes the derivation of a MADL for arsenic (inorganic oxides).

Arsenic (inorganic oxides) were listed under Proposition 65 as known to the State to cause reproductive toxicity (developmental toxicity), effective May 1, 1997. For purposes of Proposition 65, arsenic (As) oxides include arsenate and arsenite salts, arsenic trioxide, arsenic pentoxide, arsenic acid, arsenous acid and other arsenic compounds that dissociate to the oxyanion species.

The Proposition 65 listing of arsenic (inorganic oxides) was based on a finding by the Developmental and Reproductive Toxicant (DART) Identification Committee, the Proposition 65 State's qualified experts for reproductive toxicity, that the chemicals had been clearly shown by scientifically valid testing according to generally accepted principles to cause developmental toxicity. As part of its deliberations, the Committee was provided with the document "Evidence on Developmental and Reproductive Toxicity of Arsenic," developed by OEHHA (1996). OEHHA reviewed dose response data referenced that document as well as subsequent publications in preparation for MADL development.

Procedures for the development of Proposition 65 MADLs are provided in regulations (Title 22, California Code of Regulations, Sections 12801 and 12803 [22 CCR 12801 and 12803]). Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. MADLs are derived from No Observable Effect Levels (NOELs), the highest exposure levels at which no effect was observed, or Lowest Observable Effect Levels (LOELs), the lowest exposure levels at which an adverse effect was observed under the specific conditions of the study in question.

Study Selection

Relevant data on the reproductive toxicity of inorganic arsenic have been summarized in the document, “Evidence on Developmental and Reproductive Toxicity of Arsenic” (OEHHA 1996). In addition, studies published from 1996 to 2003 were identified through literature searches and reviewed. During this time, a number of studies were published of health effects in populations worldwide exposed to elevated concentrations of arsenic in drinking water. Studies relevant to reproductive and developmental toxicity are identified in the Appendix.

The NOEL for MADL development is required to be based on the most sensitive study deemed to be of sufficient quality (22 CCR Section 12803(a)(4)). A recent study from the human literature of the effects of elevated drinking water arsenic on pregnancy outcome in Bangladesh (Ahmad et al., 2001) was considered to be of sufficient quality and to provide adequate exposure information. Studies from the animal literature indicated that higher doses of arsenic were required to produce developmental toxicity in animals than in the human study. The lowest doses producing developmental toxicity in rodent studies were 8-13 mg As/kg/d as compared to 0.017 mg As/kg/d (0.986 mg/d in a 58 kg woman) in the study of Ahmad et al. (2001). This is consistent with reviews (ATSDR, 2001) concluding that humans are more sensitive to arsenic toxicity than laboratory animal species, probably due to well-documented species differences in arsenic absorption, distribution, metabolism, and excretion (Vahter, 1994). A recent study on transplacental carcinogenesis in mice by Waalkes et al. (2003) showed a high incidence of cancer in adult animals that had been exposed to arsenic only on days 8 to 18 of gestation. Following the methodology outlined in 22 CCR 12801, human studies currently provide the most sensitive and appropriate basis for MADL development and the study by Ahmad et al. (2001) provides the specific basis for MADL development. However, the Waalkes et al. study may prove to be an important contribution to arsenic risk assessment, by providing data for estimating cancer risks from transplacental exposure.

Three additional studies (Borzsonyi et al.,1992; Hopenhayn-Rich et al., 2000; and Yang et al., 2003) also found positive associations between arsenic drinking water exposure and adverse reproductive outcomes (spontaneous abortion, stillbirth, low birth weight). These studies provide supportive evidence for the findings of the study by Ahmad et al. (2001). However, these studies were not used for MADL development: two of the studies (Borzsonyi et al., 1992, and Hopenhayn-Rich et al., 2000) did not contain sufficient exposure information, while the third (Yang et al., 2003) did not control for potentially important covariates (e.g. gestational age).

In the historical cohort study of Ahmad et al. (2001), the incidences of three adverse pregnancy outcomes (spontaneous abortion, stillbirth, preterm birth) were determined by interviews using a questionnaire and checklist. Respondents (n=96 per group) were randomly selected from the exposed population and controls were matched for age, education and socioeconomic status. Statistical comparisons were made between a low exposure community (drinking water concentration <0.02 mg As/L) and a high exposure community (drinking water concentration >0.05 mg As/L in 85% of wells). Subgroups within the high exposure community with briefer and longer exposures (5-15 years or ≥ 15 years) were also compared. The risk of spontaneous abortion, stillbirth or preterm birth in the exposed group was more than double that of the unexposed group ($p < 0.05$, Fisher's exact test, one-sided). Comparisons of these adverse pregnancy outcomes between shorter and longer exposures were also statistically significant.

Arsenic concentrations in drinking water of the high exposure community were obtained from an earlier survey of 284 tube wells using hydride generation atomic absorption spectrophotometry (Ahmad et al., 1999). The average arsenic concentration of the wells was 0.240 mg/L. Using a daily consumption of 3.1 L of water and a woman's average weight of 43.2 kg, both determined by Ahmad et al. (1999), the average intake associated with developmental toxicity in the Ahmad et al. (2001) study would be 1.0 mg/d for a 58 kg woman.

MADL Calculation

Ahmad et al. (2001) stated that the average drinking water arsenic concentration was 0.24 mg/L in the community used to select respondents for the exposed population. In a previous study, Ahmad et al. (1999) determined the highest average drinking water consumption in a similar population to be 3.1 L/d for women, and the average weight for the women to be 43.2 kg. Thus the LOEL for the study was 0. 0172 mg As/kg/d. Converted to a daily human intake for a 58 kg woman (22 CCR 12803(b)), this value corresponds to 1.0 mg As/d:

LOEL = (0.24 mg As/L x 3.1 L/d) ÷ 43.2 kg = 0.0172 mg As/kg/d

0.0172 mg As/kg/d x 58 kg = **1.0 mg As/d**

Since there was only one exposed group, the study had no NOEL. When the data do not allow the determination of a NOEL, the LOEL is divided by 10 to establish a NOEL for purposes of assessment (22 CCR 12803(a)(7)).

NOEL = 1.0 mg As/d ÷ 10 = **0.10 mg As/d**

The MADL is derived by dividing the NOEL by one thousand (1,000) to arrive at the maximum allowable dose level (22 CCR Section 12801(b)(1)).

MADL = 0.10 mg As/d ÷ 1000 = 0.10 μg As/d = **0.10 μg As/d**

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Appendix

Additional references reviewed since publication of "Evidence on Developmental and Reproductive Toxicity of Arsenic" (OEHHA, 1996)

The following studies were identified in a literature search conducted to identify relevant literature published subsequent to the development of the OEHHA (1996) review. They were reviewed along with the studies in OEHHA (1996) to evaluate the most appropriate basis for derivation of a MADL.

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